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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/558,276	11/18/2005	Thomas Wisniewski	05986/100M536-US1	3691
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DARBY & DARBY P.C. P.O. BOX 770 Church Street Station New York, NY 10008-0770			EXAMINER BOESEN, AGNIESZKA	
			ART UNIT 1648	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/558,276	<b>Applicant(s)</b> WISNIEWSKI ET AL.	
	<b>Examiner</b> AGNIESZKA BOESEN	<b>Art Unit</b> 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,22,23,28-31,33-37,40,45,46,51-53,56 and 920 is/are pending in the application.
- 4a) Of the above claim(s) 11-13,15-19,29-31,33-37 and 40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,9,10,20,22,23,28,45,46,51-53 and 56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/26/2010</u> .   | 6) <input type="checkbox"/> Other: _____                          |

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## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 26, 2010 has been entered.

Claims 1, 9, 10 and 20 have been amended. Claims 54-55 have been canceled. Rejections of canceled claims are moot. New claim 56 has been added. Claims 11-13, 15-19, 29-31, 33-37 and 40 are withdrawn because they are drawn to non-elected inventions. Claims 1, 3, 4, 9, 10, 20, 22, 23, 28, 45, 46, 51-53 and 56 are under consideration in this Office action.

### ***Claim Rejections - 35 USC § 102***

Rejection of Claim 1 under 35 U.S.C. 102(e) as being anticipated by Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) present in the Office action of 12/28/2007 **is withdrawn** in view of Applicant's amendment.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

### **New Rejection**

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**Rejection of Claim 1 under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) in view of Gizurarson et al. (US Patent 6,514,503 B1) present in the Office action on 8/7/2008 is reinstated because of Applicant's amendment adding back the limitation "the composition is suitable for mucosal administration".**

Bachman et al. teach a composition comprising a mammalian prion protein, wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4 and represents the elk prion protein (see SEQ ID NO: 82 of the sequence listing, and claims 1, 14, and 15).

Bachman et al. disclose compositions comprising mammalian prion proteins formulated with an adjuvant aluminium hydroxide eliciting humoral immune response and alum as a pharmaceutically acceptable excipient –an antigen carrier (see [0035], [0080], and Example 15).

Bachman expressly teaches inducing Th-2-type immune responses because Bachman teaches that immunization comprising administering VLPs together with the prion proteins efficiently induces the antibody immune responses (see Abstract, [0012], [0035], [0037], [0079], [0263], [0443], [0444], [0447], Example 17 and Figure 3). Bachman, in fact, focuses on inducing prion specific antibody immune responses and does not disclose inducing CTL responses.

[0003] The compositions of the invention are useful in the production of vaccines for the treatment of prion diseases and as a pharmaccine to prevent or cure prion diseases and to efficiently induce immune responses, **in particular antibody responses** (...)

[0037] Three immunizations with mPrPs-Q.beta. **were sufficient to induce an anti-PrP antibody response in wild-type and Prnp<sup>0/0</sup> mice** lasting for two and a half months. Moreover, the anti-PrP serum antibody levels raised by mPrPs-Q.beta. were slightly higher in Prnp<sup>0/0</sup> than wild-type mice. Compared to 6H4 .mu.l-transgenic mice, immunization with mPrPs-Q.beta. resulted in an increased anti-PrP response.

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It is well known in the art that the Th-2-type helper cells stimulate B cell to produce antibodies and that activated B cells stimulate Th-2-type helper cells which induce a switch from IgM to IgG antibody production in B cells, as evidenced by Bachman (see [0012]).

Bachman does not teach a composition is suitable for mucosal administration and elicits a humoral immune response that is predominantly associated with an IgA response when administered to mucosal immune system.

Gizurarson et al. teach compositions comprising prion proteins suitable for mucosal administration (see claims 1-28 and columns 2-6). Gizurarson teaches that his compositions formulated for mucosal administration provide enhanced adhesion of the antigen to the mucosal membrane and enhance absorption of the antigen through the mucus membrane, and that the mucosal administration provides the ability to elicit both a systemic (e.g., antibodies of the IgG isotype) and a local (e.g., secretory antibodies of the IgA isotype) immune response in the recipients of the composition without causing unacceptable irritation of the epithelial membrane (see column 2, lines 48-65).

It would have been obvious to provide Bachman's composition comprising prion proteins for mucosal administration as taught by Gizurarson.

One would have been motivated to provide Bachman's composition formulated for mucosal administration because Gizurarson teaches that his compositions formulated for mucosal administration provide enhanced adhesion of the antigen to the mucosal membrane and enhance absorption of the antigen through the mucus membrane, and that the mucosal administration provides the ability to elicit both a systemic (e.g., antibodies of the IgG isotype) and a local (e.g., secretory antibodies of the IgA isotype) immune response in the recipients of

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the composition without causing unacceptable irritation of the epithelial membrane (see column 2, lines 48-65).

One would have had a reasonable expectation of success to provide prion composition for mucosal administration because the guidance for providing such compositions is available in the art.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

**Claim 9 and new claim 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Application Publication No.: 2003/0219459 A1) and Gizurarson et al. (US Patent 6,514,503 B1) as applied to claim 1 and further in view of Clemens et al. (US Patent 6,440,423 B1) and Kleanthous et al. (US Patent 6,585,975 B1).**

Bachman et al. and Gizurarson et al. teach compositions comprising a mammalian prion protein for mucosal administration, as discussed above. Neither Bachman et al. nor Gizurarson et al. teach the composition wherein the prion protein is covalently attached to the cholera toxin subunit B.

Clemens et al. teach cholera toxin subunit B as an effective adjuvant comprised in vaccine compositions comprising viral or bacterial antigens (see the entire document, particularly claims 1-7 and column 4, lines 28-51). It is noted that Clemens et al. also teach another adjuvant species recited in claim 9, the heat-labile enterotoxin (LT) (see column 9, lines 60-67 and column 10, lines 1-67). Clemens et al. do not expressly teach covalent attachment of cholera toxin subunit B to the antigenic protein. Kleanthous et al. teach covalent attachment of cholera

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toxin subunit B adjuvant to the antigenic protein (column 5, lines 1-20). Kleanthous et al. teach deliver vehicle aluminum hydroxide (column 6, lines 3-8).

It would have been *prima facie* obvious to covalently attach cholera toxin subunit B to the prion protein. One would have been motivated to covalently attach Clemens' cholera toxin subunit B to Bachman's prion protein, because Clemens' teach that cholera toxin subunit B adjuvant allows for improved mode of oral immunization and development of serum and mucosal antibodies against pathogenic microorganisms and that the cholera toxin subunit B is useful in combination with any specific antigen where a specific neutralizing antibody response would be beneficial in ablating the disease state associated with the antigen (see column 9, lines 5-26).

One would have had a reasonable expectation of success to provide a pharmaceutical composition comprising prion protein covalently attached to the cholera toxin subunit B, because a covalent attachment of cholera toxin subunit B to antigens of interest has been successfully practiced in the art as evidenced by Kleanthous et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

**Rejection of Claim 3** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) in view of Gizurarson et al. (US Patent 6,514,503 B1) and further in view of Peretz et al. (Nature 2001, Vol. 412, p. 739-743) and Kaneko et al. (JMB, 2000, Vol. 295, p. 997-1007) **is maintained.**

**Rejection of Claim 4** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) and Gizurarson et al. (US Patent

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6,514,503 B1) as applied to claim 1 and further in view of Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285, in IDS of 11/18/2005) **is maintained.**

**Rejection of claim 9** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Application Publication No.: 2003/0219459 A1) and Gizurarson et al. (US Patent 6,514,503 B1) as applied to claim 1 and further in view of Clemens et al. (US Patent 6,440,423 B1) and Kleanthous et al. (US Patent 6,585,975 B1) **is withdrawn** in view of Applicant's amendment.

**Rejection of claim 10** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Application Publication No.: 2003/0219459 A1) and Gizurarson et al. (US Patent 6,514,503 B1) as applied to claim 1 and further in view of Clemens et al. (US Patent 6,440,423 B1) and Kleanthous et al. (US Patent 6,585,975 B1) **is maintained.**

**Rejection of Claims 20, 22 and 28** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1), Gizurarson et al. (US Patent 6,514,503 B1) and Lu et al. (US Patent 5,733,760) and further in view of Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) **is maintained.**

**Rejection of Claims 23 and 46** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1), Gizurarson et al. (US Patent 6,514,503 B1) and Lu et al. (US Patent 5,733,760) as applied to claims 22 and further in view of Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) **is maintained.**

**Rejection of Claim 45** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1), Gizurarson et al. (US Patent 6,514,503 B1 ) and Lu et al. (US Patent 5,733,760) and Chabalgoity et al. (Vaccine, 2001, Vol.



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19, p. 460-469, in IDS of 11/18/2005) further in view of Peretz et al. (Nature 2001, Vol. 412, p. 739-743) and Kaneko et al. (JMB, 2000, Vol. 295, p. 997-1007) **is maintained.**

**Rejection of Claims 51 -53** under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1), Gizurarson et al. (US Patent 6,514,503 B1) and Lu et al. (US Patent 5,733,760), Kotloff (Infection and Immunity, 2002, Vol. 70, p. 2016-2021) and further in view of Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) Lu et al. (US Patent 5,733,760) Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) Peretz et al. (Nature 2001, Vol. 412, p. 739-743) and Kaneko et al. (JMB, 2000, Vol. 295, p. 997-1007) **is maintained.**

***Response to Applicant's arguments***

Applicant's arguments have been fully considered but fail to persuade. Applicant amended claim 1 to add the limitations: A composition comprising an isolated non-infectious, non-pathogenic mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein and a delivery vehicle or carrier, wherein the composition is suitable for mucosal administration and, when introduced to a mammal's mucosal immune system elicits a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids when introduced to a mammalian mucosal immune system and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response.

Applicant argues Bachmann discloses compositions comprising VLPs which induce a potent Th-1-type CTL response, not "a primarily Th-2 immune response ... not associated with a

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primarily Th-1-type CTL response" as required by Claim 1, when administered mucosally.

Applicant argues that the functional property of the immunogenic compositions of the present invention is very important, because mucosal Th-1- type cytotoxic T-lymphocyte (CTL) responses can be very harmful to the host. Applicant states that since the presently claimed compositions elicit a mucosal humoral immune response against an endogenous prion protein when administered mucosally, any associated Th-1-type CTL response would lead undesirably to autoimmune toxicity. Applicant states that Th-1 mediated phagocytosis of infectious prions, which are resistant to degradation, may speed up prion infection, instead of preventing it.

Applicant refers to Wisniewski et al., Rev. sci. tech. Off. int. Epiz., 2007, 26(1): 243-251, 2007; Aucoeur et al., 2000, 96: 79-85; Wisniewski and Boutajangout, Mount Sinai Journal of Medicine, 2010, 77: 17-31. Applicant also cites Shi et al. (J. Virol., 2001, 75(21): 10139-10148; attached as Exhibit D) who discloses that VLPs induce strong Th-1-type CTL responses following mucosal immunization.

In response to Applicant's arguments the Examiner notes that the functional language regarding inducing the Th-2-type immune responses recited in the present claims is viewed as intended use of the claimed composition. Thus, the recitation of "elicits a primarily Th-2-type immune response" in the claims confers no further substance to the claim and is given little patentable weight (see *In re Pearson*, 494 F.2<sup>nd</sup> 1399, 1403, 181 USPQ 641, 664 (CCPA 1974)).

Even if the functional language recited in the present claims was given patentable weight the Examiner respectfully disagrees with Applicant contention and the interpretation of the teachings in Bachman. Examiner acknowledges the references cited by Applicant discussing VLPs inducing CTL responses, however Examiner disagrees with Applicant that Bachman

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teaches the induction of prion specific Th-1-type CTL responses without teaching inducing Th-2-type immune responses. Bachman expressly teaches inducing Th-2-type immune responses because Bachman teaches that immunization comprising administering VLPs together with the prion proteins efficiently induces the antibody immune responses (see Abstract, [0012], [0035], [0037], [0079], [0263], [0443], [0444], [0447], Example 17 and Figure 3). Bachman, in fact, focuses on inducing prion specific antibody immune responses and does not disclose inducing CTL responses.

[0003] The compositions of the invention are useful in the production of vaccines for the treatment of prion diseases and as a pharmaccine to prevent or cure prion diseases and to efficiently induce immune responses, **in particular antibody responses** (...)

[0037] Three immunizations with mPrPs-Q.beta. **were sufficient to induce an anti-PrP antibody response in wild-type and Prnp<sup>0/0</sup> mice** lasting for two and a half months. Moreover, the anti-PrP serum antibody levels raised by mPrPs-Q.beta. were slightly higher in Prnp<sup>0/0</sup> than wild-type mice. Compared to 6H4 .mu.l-transgenic mice, immunization with mPrPs-Q.beta. resulted in an increased anti-PrP response.

It is well known in the art that the Th-2-type helper cells stimulate B cell to produce antibodies and that activated B cells stimulate Th-2-type helper cells which induce a switch from IgM to IgG antibody production in B cells, as evidenced by Bachman (see [0012]).

[0012] One way to improve the efficiency of vaccination is to increase the degree of repetitiveness of the antigen applied. Unlike isolated proteins, viruses induce prompt and efficient immune responses in the absence of any adjuvants both with and without T-cell help (Bachmann and Zinkernagel, Ann. Rev. Immunol. 15:235-270 (1991)). Although viruses often consist of few proteins, they are able to trigger much stronger immune responses than their isolated components. For B-cell responses, it is known that one crucial factor for the immunogenicity of viruses is the repetitiveness and order of surface epitopes. Many viruses exhibit a quasi-crystalline surface that displays a regular array of epitopes which efficiently crosslinks epitope-specific immunoglobulins on B cells (Bachmann and Zinkernagel, Immunol. Today 17:553-558 (1996)). This crosslinking of surface immunoglobulins on B cells is a strong activation signal that directly induces cell-cycle progression and the production of IgM antibodies. Further, **such triggered B cells are able to activate T helper cells, which in turn induce a switch from IgM to IgG antibody production in B cells and the generation of long-lived B cell memory-the goal of any vaccination** (Bachmann and Zinkernagel, Ann. Rev.

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Immunol. 15:235-270 (1997)). Viral structure is even linked to the generation of anti-antibodies in autoimmune disease and as a part of the natural response to pathogens (see Fehr, T., et al., J Exp. Med. 185:1785-1792 (1997)). Thus, antibodies presented by a highly organized viral surface are able to induce strong anti-antibody responses.

Thus contrary to Applicant's contention, Bachman teaches primarily inducing Th-2-type immune responses and therefore teaches the limitations of the present claims.

Applicant argues that the secondary references do not cure the deficiency of Bachmann because they do not disclose or suggest any compositions which are recited in the present claims.

In response the Examiner respectfully disagrees. As discussed on the record, Gizurarson et al. teach compositions comprising prion proteins suitable for mucosal administration (see claims 1-28 and columns 2-6). Gizurarson teaches that his compositions formulated for mucosal administration elicit both a systemic (e.g., antibodies of the IgG isotype) and a local (e.g., secretory antibodies of the IgA isotype) immune response in the recipients (see column 2, lines 48-65). The antibody immune response do not occur without Th-2-type immune responses, as discussed above. Bachman provides evidence (see [0012]) that antibody responses necessarily require Th-2-type helper cells to stimulate B cell to produce antibodies. Thus because Gizurarson teaches inducing antibody responses Gizurarson necessarily teaches Th-2-type immune responses.

Applicant argues that the secondary references do not cure the deficiency of Bachmann because neither Clemens, Kleanthouse, Lu nor Chabalgoity disclose or suggest compositions recited in the present claims. In response, the Examiner notes that Clemens, Kleanthouse, Lu and Chabalgoity are cited in the rejections of record because they disclose the limitations of the dependent claims, as discussed on the record.

Thus in view of the foregoing the rejections are maintained.

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***Conclusion***

No claim is allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/  
Examiner, Art Unit 1648